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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/541,348	04/03/00	CHEN	J 90,057-G

EXAMINER

WANG, A

ART UNIT	PAPER NUMBER
1635	9

DATE MAILED: 08/13/01

522306
MCDONNELL BOEHNEN HULBERT & BERGHOFF
300 SOUTH WACKER DRIVE
SUITE 3200
CHICAGO IL 60606

HM12/0813

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

PTO-90C (Rev.11/00)

1- File Copy

Office Action Summary	Application No.	Applicant(s)	
	09/541,848	CHEN ET AL.	
	Examiner	Art Unit	
	Andrew Wang	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-29 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-29 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

KATRINA TURNER
PATENT ANALYST

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)
16) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
18) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other:

DETAILED ACTION

1. Applicants sequence listing filed 2 February 2001 has been and received and entered into the instant application.

2. Applicants' priority claim to application number 08/916,834, in the first line of the specification, appears to be incorrect since it appears that applicants intend to claim priority to application number 08/916,384. Applicants should note that the first line of the specification has been corrected by the examiner to claim priority to 08/916,**384** instead of 08/916,**834**. Applicant is not required to amend the specification in a subsequent response.

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-29 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 16-43 of copending Application No. 09/383,507. Although the conflicting claims are not identical, they are not patentably distinct from each other because the instantly claimed invention, drawn to a method of administering an antisense oligonucleotide targeted to MDM2 that increases activated intracellular p53 and inhibits tumor growth would be embraced by the methods claimed by 09/383,507also drawn to methods of inhibiting MDM2 by administering antisense oligos to inhibit tumor growth and increasing activated intracellular p53.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

3. Claim 10 is rejected under 35 U.S.C. 102(b) as being anticipated by WO 93/20238.

The invention of the above claims is drawn to a method of activating p53 in a tumor cell comprising contacting said cells with an antisense oligo targeted to MDM2.

WO 93/20238 discloses that the MDM2 can be inhibited by antisense oligos thereby allowing p53 regulated cellular apoptosis.

Therefore, as discussed above, WO 93/20238 anticipates all of the limitations of the above claim.

4. Claims 10 and 11 are rejected under 35 U.S.C. 102(b) as being anticipated by Kondo et al.

The invention of the above claims is drawn to a method of activating p53 in a cell or enhancing DNA-damage induced activation of p53 in tumor cells comprising contacting said cells with a DNA-damaging agent and an antisense oligo targeted to MDM2.

Kondo et al. disclose the administration of MDM2 antisense oligos to glioblastoma cells wherein the cells were also treated with cisplatin, a DNA damaging agent. It was further disclosed that cisplatin caused a concomitant increase in p53 expression.

Therefore, as discussed above, Kondo et al. anticipate all of the limitations of the above claims.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

5. Claims 10-12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kondo et al. in view of Clark et al.

The invention of the above claims is drawn to a method of enhancing DNA-damage induced activation of p53 in tumor cells comprising contacting said cells with camptothecin and an antisense oligo targeted to MDM2.

Kondo et al. is relied upon as discussed above in the 102(b) rejection. Kondo does not teach the administration of camptothecin as the DNA damaging agent.

Clark et al. disclose the administration of camptothecin in the treatment of pancreatic cancer.

It would have been obvious to one of ordinary skill in the art to use camptothecin, in lieu of cisplatin, in the methods of Kondo since both agents are recognized to be DNA damaging agents and thus be able to used interchangeably. Moreover, one would have

had a reasonable expectation of success in using camptothecin since both camptothecin and cisplatin are used as anti-cancer drugs.

Therefore, as discussed above, the invention of the above claims, would have been *prima facie* obvious to one of ordinary skill in the art over Kondo et al. in view of Clark et al. without evidence to the contrary.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 1-29 are rejected under 35 U.S.C. 112, first paragraph, because the specification is only enabling for a method of inhibiting tumor cells, in vitro, using MDM2 antisense oligos and a method of inhibiting tumor cells in vitro or in vivo using SEQ ID NO: 28 or 47. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The invention of the above claims is drawn to a method of inhibiting tumor growth by administering a MDM2 antisense oligo or a combination of a chemotherapeutic and a MDM2 antisense oligo to a mammal. The invention is further drawn to administering antisense oligos targeted to SEQ ID NO: 2-4, 7-11, and 13-24 of the MDM2 transcript as well as antisense oligos comprising SEQ ID NO: 27-46.

The specification teaches the screening of antisense oligos that demonstrated inhibitory activity towards MDM2 in cells in culture and further demonstrates that SEQ ID NO: 28 and 47 reduced xenoplanted tumor size in mice when administered intraperitoneally. Although the specification does provide guidance for the use of SEQ ID NO: 28 and 47, in vivo, such a disclosure taken together with the general guidance provided in the specification would not enable the breadth sought since the specification does not demonstrate any other MDM2 antisense oligo exhibiting in vivo activity alone or in combination with a chemotherapeutic. Without further demonstration of additional oligos in an in vivo methodology one of skill in the art would not accept the success of two antisense oligos, SEQ ID NO: 28 and 47, would be correlative with the genus sought as is discussed below.

The specification as filed does not enable the therapeutic use of any antisense oligo other than SEQ ID NO: 28 and 47 since the clinical application of antisense therapy is a highly unpredictable art due to obstacles that still face antisense therapy as summarized by Agrawal who states the following: " [t]here are two crucial parameters in drug design: the first is the identification of an appropriate target in the disease process, and the second is finding an appropriate molecule that has specific recognition and affinity for the target, thereby interfering in the disease process" (page 376); "[o]ligonucleotide must be taken up by cells in order to be effective. [s]everal reports have shown that efficient uptake of oligonucleotides occurs in a variety of cell lines, including primary cells whereas other reports indicate negligible cellular uptake of oligonucleotides. [c]ellular uptake of oligonucleotides is a complex process; it depends

on many factors, including the cell type, the stage of the cell cycle, the concentration of serum.[i]t is therefore, difficult to generalize that all oligonucleotides are taken up in all cells with the same efficiency." (Page 378); "[a]ny antisense activity observed in such artificial systems [cell culture] should be scrutinized carefully with respect to the disease process and its applicability to *in vivo* situations." (Page 379). Branch further elucidates the unpredictability of oligo therapy by stating that "the value of a potential antisense drug can only be judged after its intended clinical use is known, and quantitative information about its dose-response curves and therapeutic index is available" (page 46, second column) and "internal structures of target RNAs and their associations with cellular proteins create physical barriers, which render most potential binding sites inaccessible to antisense molecules" (page 45, third column). Additionally, in a recently published review of the potential use of antisense oligos as therapeutic agents, Gewirtz et al. teach that the inhibitory activity of an oligo depends unpredictably on both the sequence and structure of the nucleic acid target site and the ability of the oligo to reach its target (page 3161, second and third columns). Gewirtz et al. and Branch conclude by observing that, "the antisense approach has generated controversy with regard to mechanism of action, reliability, and ultimate therapeutic utility" and "that efforts should be increased...to learn how they may be used successfully in the clinic" (page 3162, middle column, last paragraph) and "non-antisense effects are not currently predictable, rules for rational design cannot be applied to the production of non-antisense drugs, These effects must be explored on a case-by-case basis." (page 50), respectively.

Thus, the specification fails to provide adequate guidance for one of skill in the art to overcome the unpredictability and challenges in the antisense therapy art that are exemplified in the references above. Moreover, the instant specification fails to provide one of skill in the art guidance for the selection of pharmaceutical antisense compounds without undue trial and error experimentation since it is clear from the references above that in vitro and cellular screening do not correlate with pharmaceutical antisense compounds that function in an *in vivo* environment.

7. The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because:
The specification to which the oath or declaration is directed has not been adequately identified. See MPEP § 601.01(a). Applicants have inadvertantly identified the incorrect application as noted above.

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Andrew Wang whose telephone number is 703-306-3217. The examiner can normally be reached on Monday thru Thursday, 6:30 a.m.-5:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader can be reached on 703-308-0447. The fax phone numbers for the organization where this application or proceeding is assigned are 703-

308-4242 for regular communications and 703-308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Andrew Wang
Primary Examiner
Art Unit 1635

AJW
August 8, 2001